**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use INVOKANA® safely and effectively. See full prescribing information for INVOKANA.**

**INVOKANA (canagliflozin) tablets, for oral use**
**Initial U.S. Approval: 2013**

**WARNING: LOWER LIMB AMPUTATION**
***See full prescribing information for complete boxed warning.***

- **In patients with type 2 diabetes who have established cardiovascular disease (CVD) or at risk for CVD, INVOKANA has been associated with lower limb amputations, most frequently of the toe and midfoot; some also involved the leg (5.1)**
- **Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving INVOKANA for infections or ulcers of the lower limbs, and discontinue if these occur. (5.1)**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Boxed Warning | 07/2017 |
| Warnings and Precautions (5.1) | 07/2017 |

**----------INDICATIONS AND USAGE----------**
INVOKANA is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1)

**Limitation of Use:**
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1)

**----------DOSAGE AND ADMINISTRATION----------**
- The recommended starting dose is 100 mg once daily, taken before the first meal of the day (2.1)
- Dose can be increased to 300 mg once daily in patients tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 $m^2$ or greater and require additional glycemic control (2.1)
- Assess renal function before initiating and periodically thereafter. (2.2)
- Limit the dose of INVOKANA to 100 mg once daily in patients who have an eGFR of 45 to less than 60 mL/min/1.73 $m^2$ (2.2)
- Initiation or use of INVOKANA is not recommended if eGFR is below 45 mL/min/1.73 $m^2$ (2.2)

**----------DOSAGE FORMS AND STRENGTHS----------**
Tablets: 100 mg, 300 mg (3)

**----------CONTRAINDICATIONS----------**
- History of serious hypersensitivity reaction to INVOKANA (4)
- Severe renal impairment, ESRD, or on dialysis (4)

**----------WARNINGS AND PRECAUTIONS----------**
- Lower Limb Amputation: See boxed warning (5.1)
- Hypotension: Before initiating INVOKANA, assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, or if on diuretics, ACEi, or ARB. Monitor for signs and symptoms during therapy (5.2)
- Ketoacidosis: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue INVOKANA, evaluate and treat promptly. Before initiating INVOKANA, consider risk factors for ketoacidosis. Patients on INVOKANA may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis (5.3)
- Acute kidney injury and impairment in renal function: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy (5.4)
- Hyperkalemia: Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia (2.2, 5.5, 6.1, 8.6)
- Urosepsis and Pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.6)
- Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with INVOKANA (5.7)
- Genital mycotic infections: Monitor and treat if indicated (5.8)
- Hypersensitivity reactions: Discontinue INVOKANA and monitor until signs and symptoms resolve (5.9)
- Bone fracture: Consider factors that contribute to fracture risk before initiating INVOKANA (5.10)
- Increased LDL-C: Monitor LDL-C and treat if appropriate (5.11)

**----------ADVERSE REACTIONS----------**
- Most common adverse reactions associated with INVOKANA (5% or greater incidence): female genital mycotic infections, urinary tract infection, and increased urination (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

**----------DRUG INTERACTIONS----------**
- UGT inducers (e.g., rifampin): Canagliflozin exposure is reduced. Consider increasing dose from 100 mg to 300 mg (2.3, 7.1)
- Digoxin: Monitor digoxin levels (7.2)

**----------USE IN SPECIFIC POPULATIONS----------**
- Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- Lactation: INVOKANA is not recommended when breastfeeding (8.2)
- Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume (5.2, 8.5)
- Renal impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function (2.2, 5.4, 8.6)
- Hepatic impairment: Not recommended with severe hepatic impairment (8.7)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 07/2017**

**FULL PRESCRIBING INFORMATION: CONTENTS***

*Sections or subsections omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION**

**WARNING: LOWER LIMB AMPUTATION**

- **An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA use was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established cardiovascular disease (CVD) or were at risk for CVD.**
- **Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs.**
- **Before initiating, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.**
- **Monitor patients receiving INVOKANA for infection, new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue if these complications occur *[see Warnings and Precautions (5.1)]*.**

## 1 INDICATIONS AND USAGE

INVOKANA® (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14)]*.

Limitation of Use

INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

The recommended starting dose of INVOKANA (canagliflozin) is 100 mg once daily, taken before the first meal of the day. In patients tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 $m^2$ or greater and require additional glycemic control, the dose can be increased to 300 mg once daily *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.2), and Patient Counseling Information (17)]*.

In patients with volume depletion, correcting this condition prior to initiation of INVOKANA is recommended *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5 and 8.6), and Patient Counseling Information (17)]*.

### 2.2 Patients with Renal Impairment

Assessment of renal function is recommended prior to initiation of INVOKANA and periodically thereafter.

The dose of INVOKANA is limited to 100 mg once daily in patients with moderate renal impairment with an eGFR of 45 to less than 60 mL/min/1.73 $m^2$.

Initiation of INVOKANA is not recommended in patients with an eGFR less than 45 mL/min/1.73 $m^2$.

Use of INVOKANA is not recommended when eGFR is persistently less than 45 mL/min/1.73 $m^2$ *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*.

INVOKANA is contraindicated in patients with an eGFR less than 30 mL/min/1.73 $m^2$ *[see Contraindications (4)]*.

### 2.3 Concomitant Use with UDP-Glucuronosyl Transferase (UGT) Enzyme Inducers

If an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, consider increasing the dosage to 300 mg once daily in patients currently tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 $m^2$ or greater and require additional glycemic control *[see Drug Interactions (7.1)]*.

Consider another antihyperglycemic agent in patients with an eGFR of 45 to less than 60 mL/min/1.73 $m^2$ receiving concurrent therapy with a UGT inducer.

## 3 DOSAGE FORMS AND STRENGTHS

- INVOKANA 100 mg tablets are yellow, capsule-shaped, film-coated tablets with “CFZ” on one side and “100” on the other side.
- INVOKANA 300 mg tablets are white, capsule-shaped, film-coated tablets with “CFZ” on one side and “300” on the other side.

## 4 CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA, such as anaphylaxis or angioedema *[see Warnings and Precautions (5.9) and Adverse Reactions (6.1, 6.2)]*.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 $m^2$), end stage renal disease (ESRD), or patients on dialysis *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Lower Limb Amputation

An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA use was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. In CANVAS, INVOKANA-treated patients and placebo-treated patients had 5.9 and 2.8 amputations per 1000 patients per year, respectively. In CANVAS-R, INVOKANA-treated patients and placebo-treated patients had 7.5 and 4.2 amputations per 1000 patients per year, respectively. The risk of lower limb amputations was observed at both the 100 mg and 300 mg once daily dosage regimens. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively *[see Adverse Reactions (6.1)]*.

Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA in the two trials). Some patients had multiple amputations, some involving both lower limbs.

Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

Before initiating INVOKANA, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving INVOKANA for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKANA if these complications occur.

### 5.2 Hypotension

INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions (6.1)]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 $m^2$), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

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